

PATENT SPECIFICATION

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(54) COMPOSITIONS FOR REMINERALIZING TOOTH ENAMEL

(71) We, THE PROCTER & GAMBLE COMPANY, a Corporation organised and existing under the laws of the State of Ohio, United States of America of 301 East Sixth Street, Cincinnati, Ohio 45202, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the remineralization of dental enamel by means of forming a metastable solution of calcium ions, phosphate ions, and optionally, certain other additional desirable ions in the mouth, in order to combat dental caries.

It is well known in the dental art that dental caries begins as a sub-surface demineralization ("white spots") of the dental enamel and that remineralization or recalcification (i.e. remineralization) may be of importance in retarding or arresting dental caries. It is especially desirable to accomplish remineralization by precipitating calcium phosphate into the tooth surface. British Patent Specification No. 1,452,125 teaches a method of remineralizing sub-surface dental enamel in which two compositions containing, respectively, calcium cations and phosphate anions, are sequentially applied to the teeth in order to precipitate calcium phosphate into the sub-surface of the dental enamel. This method, while successful, requires sequential application of the respective solutions. An improvement over this sequential technique is disclosed in British Specification No. 1,488,859 whereby a metastable solution of calcium and phosphate ions at a pH from 2 to 5 is prepared and applied to the teeth within a few minutes after preparation. The calcium and phosphate ions remain dissolved in such a solution for a short period of time, thus allowing both ions to be applied simultaneously to the oral cavity, wherein

the ions stay in solution for a sufficient length of time to migrate into the sub-surface of the dental enamel before precipitating as calcium phosphate. It is apparent, however, that in the practice of the invention of Specification No. 1,488,859 the calcium ion solution and the phosphate ion solution must be stored separately until just prior to use, as for example, in a dual-chambered tube or bottle. Other prior art references which are generally relevant to the field of remineralization of dental enamel are U.S. Patents No. 1,222,144, No. 2,154,168 and No. 3,679,630.

It is the primary object of the present invention to provide a stable, unitary composition which can be stored for long periods of time and which can be introduced into the oral cavity to remineralize dental enamel.

The present invention provides an anhydrous composition for the remineralizing of demineralized dental enamel comprising:

(A) a calcium salt having a solubility in water of at least 0.07% by weight at 100°C;

(B) a phosphate salt (as hereinafter defined) having a solubility in water of at least 0.07% by weight at 100°C; and

(C) the balance, anhydrous ingredients suitable for use in the oral cavity; wherein the molar ratio of calcium to phosphate is from 0.01:1 to 100:1, and wherein said composition, when dispersed in water at a concentration of 1 part by weight of composition to 2 parts by weight of water, produces a pH of from 2 to 5.

While not wishing to be bound by theory, it is believed that this composition, when mixed with the saliva in the mouth, or when mixed with water shortly before introduction into the mouth, forms a metastable solution of calcium ions and phosphate ions which migrate to the demineralized areas of dental enamel where they precipitate as calcium phosphates, thereby remineralizing the enamel.

For purposes of the present invention,

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the term "oral composition" refers to a product which in the ordinary course of usage is not intentionally ingested, but is retained in the oral cavity for a time sufficient to contact substantially all of the dental surfaces. Such products include, for example, dentifrices, mouthwashes, chewing gums and dental prophylaxis pastes.

The term "anhydrous" as used herein means essentially free (i.e. containing less than 1% by weight) of unbound water. The compositions herein can contain bound water, as for example, the water of hydration of various salts, so long as the water remains bound to the salt while it is in the composition.

When such a composition is placed into the mouth, a metastable solution of calcium and phosphate ions (e.g. PO_4^{3-} , HPO_4^{2-} , or H_2PO_4^-) forms in the saliva, followed by a migration of the ions into the sub-surface of the dental enamel and a precipitation of calcium phosphates into the sub-surface of the dental enamel. Alternatively, the composition can be dispersed in water shortly (i.e., within 5 minutes) before application to the oral cavity.

The calcium salts suitable for use in the compositions of the present invention can be any calcium salt which is safe for use in the oral cavity and which has a solubility of at least 0.07% by weight in water at 100°C. Examples of suitable calcium salts are calcium chloride, calcium acetate, calcium formate, calcium lactate and calcium nitrate. Likewise, the phosphate salts suitable for use in the present invention can be any of the phosphate salts having the specified solubility in water and which are suitable for use in the oral cavity. Phosphoric acid is also suitable for use, and for purposes of brevity, it will be understood that when the term "phosphate salt" is used herein, it is intended to also include anhydrous phosphoric acid. Examples of suitable phosphate salts are disodium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate and trisodium phosphate.

The compositions of the present invention preferably contain from 0.005% to 10%, most preferably from 0.01% to 5%, by weight of water-soluble calcium salt and preferably from 0.005% to 10%, most preferably from 0.01% to 5%, by weight of water-soluble phosphate salt, and the proportions of the respective salts are selected such that the molar ratio of calcium:phosphate is from 0.01 to 100 (i.e. 0.01:1 to 100:1), preferably from 0.2 to 5. The most preferred ratio is about 1.67, which is the molar ratio of calcium to

phosphate in natural tooth enamel (hydroxyapatite).

In remineralizing the teeth, the compositions of the present invention are introduced into the oral cavity in an amount so as to provide at least 0.001 g, and preferably at least 0.1 g of calcium phosphate [calculated as $\text{Ca}_3(\text{PO}_4)_2$].

In order to achieve the metastable state which is necessary to allow calcium ions and phosphate ions to coexist in solution in the mouth (i.e., without immediately precipitating), it is essential that the proper pH be obtained when the composition is placed into contact with the saliva in the mouth. It has been found that if the composition is one which will produce a pH of from 2.0 to 5.0 (preferably from 2.5 to 4), when mixed with water at a concentration of 1 part by weight composition to 2 parts by weight water, it will have the proper pH for achieving the metastable state in the mouth.

When the composition of the invention is applied to the mouth to remineralize demineralized enamel, it is necessary that the time of contact between the composition/saliva mixture which is obtained, and the teeth, be sufficiently long to allow diffusion of the ions into the demineralized sub-surface. At least about 10 seconds are required for this diffusion. The composition is preferably kept in contact with the teeth for from 10 seconds to 3 minutes. The pH will rise due to natural factors in the mouth during this period. It is believed that the rising pH causes the calcium and phosphate ions which have diffused into the enamel to precipitate as calcium phosphate, thereby accomplishing remineralization of the enamel. Although one would expect an acidic solution, such as that formed by placing the composition of the invention into the mouth, to demineralize the teeth, the metastable solution formed in accordance with the present invention, which is saturated, or supersaturated, with respect to calcium phosphate, results in remineralization instead of demineralization.

The desired pH can be obtained by incorporating into the compositions of the invention, if necessary, common acidifying agents such as those named specifically hereinafter.

In accordance with a preferred embodiment of the present invention, the compositions herein also contain from 0.005% to 10%, preferably from 0.005% to 5%, by weight of a water-soluble salt of magnesium or a heavy metal (i.e. a Group B metal, a transition metal or a rare earth metal) in addition to the calcium salt, and optionally, from 0.005% to 10%, preferably from 0.005% to 5%, by weight of a water-

soluble salt of an anion capable of forming a water-insoluble precipitate with the cations of the calcium, magnesium or any heavy metal ion salts present in the composition. By "water-insoluble" herein, a solubility of less than 0.07% by weight in water at 100°C is meant.

In considering the preferred embodiment, it is important to note that if the demineralized sub-surface dental enamel is remineralized with a precipitate which is less soluble than the original enamel, the remineralized sub-surface is more resistant to demineralization than was the original enamel. If the remineralization contemplated by this invention is carried out in accordance with the preferred embodiments, such precipitates are formed, and the remineralized enamel is more resistant to future demineralization than was the original enamel because magnesium or heavy metal cations and/or certain anions (other than phosphate), such as fluoride ions, which are capable of forming insoluble precipitates with calcium, magnesium or heavy metal cations (hereinafter also referred to as secondary anions), are incorporated into the remineralized tooth structure. If both types of ions are so incorporated (i.e., magnesium or heavy metal ions and secondary anions), the remineralized enamel is even more resistant to demineralization than if only one of these types of ion is incorporated.

Examples of the heavy metal water-soluble salts which can be used in addition to water-soluble calcium salts in the compositions of the invention include the water-soluble salts of manganese, tin, zinc, indium, aluminium, zirconium, iron, titanium, vanadium, and rare earth metals such as lanthanum and cerium. Magnesium salts can also be used. Water-soluble salts of magnesium, tin, indium, the rare earth metals and aluminium are preferred. Indium is most preferred. Suitable water-soluble salts of these metals include the halide (e.g., chloride), nitrate, sulfate, acetate, and gluconate salts. For example, suitable soluble indium salts include indium chloride, indium sulfate and indium nitrate.

Examples of anions which will react with calcium, magnesium and heavy metal cations to give desirable remineralizing precipitates, and are therefore suitable as secondary anions herein include fatty acid radicals having from 8 to 18 carbon atoms, fluoride, fluorophosphate, silicofluoride, molybdate, sulfate, tungstate, tartrate, sorbate, alkyl sulfate containing from 8 to 18 carbon atoms, carbonate and iodate. Fluoride, fluorophosphate, fatty acid radicals containing from 8 to 18 carbon atoms (e.g., laurate and stearate) and carbonate are preferred. Suitable soluble

salts of these secondary anions include the sodium, potassium, amine, ammonium and substituted ammonium salts. The most preferred secondary anion is fluoride ion. Examples of soluble fluoride salts for incorporation into the compositions herein include sodium fluoride, potassium fluoride, betaine fluoride, alanine stannous fluoride, and hexylamine fluoride.

It will be recognized by those skilled in the art that many different precipitates in addition to calcium phosphate can be formed by introducing into the oral cavity a composition made in accordance with the present invention. It is preferred that the precipitate be white in colour. Some of these precipitates may be formed by first forming an original precipitate which then further reacts to form the remineralizing precipitate. For example, a hydroxide may form first and then react further to form the corresponding oxide. It is most preferred that the ingredients of the present invention are selected so that most precipitates are calcium phosphate compounds with small amounts of indium and fluoride incorporated therein. This results in a remineralized tooth structure which is similar to the natural tooth structure with small amounts of indium and fluoride incorporated therein, resulting in increased resistance to solubility. Thus, the remineralized tooth structure will be more resistant to dental caries than was the original structure.

By employing suitable ions in the present composition, the following insoluble precipitates in addition to calcium phosphates may be formed: CaF_2 , ZnNH_4PO_4 , InPO_4 , rare earth phosphates such as lanthanum, cerium, and samarium phosphate, rare earth fluorides such as lanthanum, cerium, praseodymium, neodymium, and samarium fluorides, magnesium alkyl sulfonate wherein the alkyl group has from 6 to 18 carbon atoms, magnesium stearate, calcium stearate, zinc stearate, and aluminium phosphate.

Other precipitates contemplated by this invention are: Aluminium oxide; aluminium hydroxide; indium hydroxide; indium phosphate; lanthanum tartrate; lanthanum sorbate; lanthanum oxalate; lanthanum oxide; lanthanum tungstate; lanthanum phosphate; magnesium alkyl sulfonates such as magnesium n-decyl sulfonate, magnesium lauryl sulfonate, magnesium myristyl sulfonate, magnesium cetyl sulfonate, and magnesium n-octadecyl sulfonate; magnesium oleate; magnesium myristate; magnesium palmitate; magnesium stearate; magnesium laurate; magnesium carbonate; magnesium fluoride; magnesium phosphates; magnesium hydroxide; magnesium

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ammonium phosphate; manganese carbonate; manganese hydroxide; manganese ammonium phosphate; nickel hydroxide, laurate, myristate, palmitate, and stearate, stannous oxalate; zinc tartrate; zinc carbonate; zinc oxalate; zinc hydroxide; zinc phosphate (usually complex mixtures); zinc ammonium phosphate; zirconium hydroxide; zirconium phosphate; calcium carbonate; calcium molybdate; calcium silicate; calcium tungstate; calcium lauryl sulfonate; calcium myristyl sulfonate; calcium hexadecyl sulfonate; calcium n-octadecyl sulfonate; calcium oleate; calcium stearate; calcium tartrate; calcium aluminates; calcium hydroxide, calcium ammonium phosphate; tricalcium phosphate; dicalcium phosphate; calcium monofluorophosphate; MgHPO_4 ; $\text{Mg}_3(\text{PO}_4)_2$; MgNH_4PO_4 ; aluminium phosphates, aluminium orthophosphate; calcium phosphates; zinc phosphates, strontium phosphate; indium phosphate; tin phosphate, ceric phosphate; MoO_3 ; SiO_2 ; $\text{SiO}_2 \cdot x\text{H}_2\text{O}$; $\text{Sn}(\text{OH})_2$; $\text{SnO}_2 \cdot x\text{H}_2\text{O}$; $\text{Ti}(\text{OH})_4$; TiO_2 ; V_2O_5 ; and WO_3 . These precipitates are formed by using water-soluble salts of the appropriate cations and anions as described above.

Typically, anhydrous compositions of the present invention in the form of mouthwashes, comprise, in addition to the remineralizing salts, from 5% to 90% by weight of absolute alcohol and from 5% to 90% by weight of humectant. Typical humectants suitable for mouthwash use include edible polyhydric alcohols, for example glycerine, sorbitol, propylene glycol and polyethylene glycol (M.W. 200-900). Optionally, such compositions can also contain from 0.01% to 0.5% by weight of a sweetening agent, from 0.01% to 2.0% by weight of a flavouring agent, and from 0.1% to 1% by weight of an organic surfactant. Suitable sweetening agents are saccharin, levulose and aspartyl phenylalanine methyl ester. Suitable flavouring agents include wintergreen oil, oil of peppermint, oil of cassia, oil of anise, oil of cinnamon and mixtures thereof. Suitable organic surfactants include polyoxyethylene (20) sorbitan monoistearate, sodium lauryl sulfate and sorbitan monolaurate. Additional suitable emulsifier-surfactants are listed below in the discussion of toothpaste compositions. Since the anhydrous mouthwash compositions described above will form metastable solutions of the remineralizing salts when mixed with water, these compositions can, if desired, be mixed with water just prior (i.e., within 5 minutes) to the time of intended use.

In mouthwashes of the present invention,

it is also desirable to incorporate suspending agents to keep the undissolved particles of remineralizing salts in suspension in the composition, thus eliminating the necessity for shaking the composition prior to use. Many agents are known which can be used as suspending agents for solid particles in oral products, and can be used in the mouthwash compositions herein. Examples are caboxymethyl cellulose, finely divided silica, methyl cellulose ("Methocel MC", Dow Chemical Co.; "Methocel" is a trade mark), hydroxyethyl cellulose and natural and synthetic gums. When suspending agents are used, they are typically present at levels of from 0.1% to 1% by weight of the composition.

Anhydrous compositions of the invention in the form of toothpastes comprise, in addition to the remineralizing salts, from 0.5% to 50%, preferably from 5% to 25%, by weight of a dentifrice abrasive, from 0.2% to 5% by weight of an organic surfactant, and from 40% to 90% by weight of a humectant. Said compositions preferably also contain from 0.1% to 5% by weight of a binding agent. Suitable humectants for toothpastes include edible polyhydric alcohols such as glycerine, sorbitol, propylene glycol, polyethylene glycols having molecular weights of 200 to 900, mineral oil and paraffin oil. Optionally, other ingredients such as flavouring agents and sweeteners such as those mentioned in the foregoing discussion of mouthwashes may be added to the compositions of the invention.

Suitable abrasives include silica xerogels such as those disclosed in British Patent Specifications 1,186,706 and 1,264,292.

Other conventional toothpaste abrasives can be used in the compositions of this invention, and include beta-phase calcium pyrophosphate, zirconium silicate, calcium carbonate, dicalcium phosphate dihydrate, the thermosetting polymerized resins described in British Patent Specification 939,230. Silica aerogels and the insoluble metaphosphates such as insoluble sodium metaphosphate can be used. Mixtures of abrasives can also be used. Silica xerogel abrasives are preferred.

Suitable surfactants are those which are reasonably stable and form suds at an acid pH. Preferably, non-soap anionic or nonionic organic synthetic detergents are used. Examples of such agents are water-soluble salts of alkyl sulfate having from 10 to 18 carbon atoms in the alkyl radical, such as sodium lauryl sulfate, water-soluble salts of sulfonated monoglycerides of fatty acids having from 10 to 18 carbon atoms, such as sodium monoglyceride sulfonate, salts of C_{10} - C_{18} fatty acid amides of taurine, such

as sodium N-methyl-N-palmitoyl tauride, sodium N-coconut-acid-N-methyl taurate, salts of C₁₀—C₁₈ fatty acid esters of isothionic acid, and substantially saturated aliphatic acyl amides of saturated monoaminocarboxylic acids having 2 to 6 carbon atoms, and in which the acyl radical contains 12 to 16 carbon atoms, such as sodium N-lauryl sarcoside. Mixtures of two or more surfactants can be used.

A binding material is preferably added to thicken and provide a desirable consistency for the toothpaste compositions. Suitable thickening agents are water-soluble salts of cellulose ethers, such as sodium carboxymethyl cellulose, hydroxypropyl cellulose, and hydroxyethyl cellulose. Natural gums such as gum kafaya, gum arabic, and gum tragacanth, can also be used. Colloidal magnesium aluminium silicate, silica aerogels, both alone and in combination with ethoxylated stearates such as polyoxyethylene (20) sorbitan monoisostearate, silica xerogels, fumed silica, or other finely divided silica can be used as part of the thickening agent for further improved texture. A preferred thickening agent is xanthan gum, available from the Kelco Company.

The humectant material in a toothpaste provides a large portion of the anhydrous vehicle and maintains the paste in a soft, pliable condition. Suitable humectants include edible polyhydric alcohols such as glycerine, sorbitol, propylene glycol, polyethylene glycol having a molecular weight from 200 to 900, mineral oil and paraffin oil.

Anhydrous chewing gum compositions of the present invention comprise, in addition to the remineralizing salts, a gum base (which is a chewable plastic gum material such as natural rubber, chicle, polyvinyl acetate, ester gum, coumarone resin or paraffin wax). Optionally, humectants, flavoring agents and artificial sweetening agents such as those described hereinbefore, and sugar can also be added. Typically, chewing gum compositions of the invention comprise, in addition to the remineralizing salts, from 15% to 40% by weight of gum base, 50% to 65% by weight of sugar, 5% to 15% by weight of humectant, and 0.05% to 1.5% by weight of flavoring material. Sufficient acid or base is added, as needed, to provide a pH within the range hereinbefore specified.

As discussed hereinbefore, it is important that the compositions of the invention achieve a pH of from 2.0 to 5.0 when mixed in a preparation of 2 parts by weight of water to 1 part by weight of composition. This may require the incorporation into the

composition of an appropriate amount of an acid to achieve the desired pH. The acid must be an anhydrous liquid or solid. Suitable acids for this purpose include glycolic acid, histidine, itaconic acid, lysine, maleic acid, malonic acid, mesaconic acid, oxalacetic acid, pimelic acid, propionic acid, succinic acid, tartaric acid, malic acid, valeric acid, boric acid, selenic acid, selenous acid, glacial acetic acid, acrylic acid, adysic acid, d-alanine, allantoin, glycine, p-aminobenzoic acid, anisic acid, ascorbic acid, aspartic acid, benzoic acid, caffeic acid, cinnamic acid, citric acid, cysteine, 2,4-dinitrophenol, formic acid, fumaric acid, furoic acid, glutamic acid, and glutaric acid.

The present invention is illustrated by the following Examples.

EXAMPLE I

A toothpaste composition according to the present invention was prepared by mixing the following ingredients in the indicated proportions:

Ingredient	Parts by Weight	
Glycerine	66.30	90
Na ₂ HPO ₄	1.89	
Sodium fluoride	0.20	
Calcium chloride	2.50	
Indium (III) chloride	0.17	95
Saccharin	0.33	
Calcium pyrophosphate	20.00	
Flavour	0.96	
Igepon TC-42 (purified) ¹	1.75	100
Aerosil 200V ²	2.00	
Keltrol ³	0.20	
Polyoxyethylene (20) sorbitan monoisostearate ⁴	2.00	
Glutamic acid hydrochloride	1.70	105
	100.00	

1. A purified grade of Igepon TC-42 (Na N-coconut acid N-methyl taurate) sold by Fine Organics, Inc., Lodi, N.J.

2. Fumed silica, sold by Degussa Inc., Pigments Div., New York, N.Y. ("Aerosil" is a Trade Mark).

3. Polysaccharide xanthan gum, sold by Kelco Co., Chicago, Ill. ("Keltrol" is a Trade Mark).

4. Emsorb 6912-A, sold by Emery Industries, Cincinnati, Ohio.

This composition, when used in brushing the teeth in the normal manner, remineralizes demineralized tooth enamel and causes the enamel to be more resistant to future demineralization than it was originally.

EXAMPLE II

A chewing gum composition of the present invention is formulated as follows:

5	Ingredient	Parts by Weight
	Gum base	21.30
	Ester gum	6.40
	Coumarone resin	9.60
	Dry latex rubber	3.20
10	Paraffin wax (M.P. 180°F.)	2.10
	Sugar	64.00
	Glycerine	7.26
	Flavour	1.05
15	Calcium chloride	2.50
	Na ₂ HPO ₄	1.89
	Citric acid	2.00
		100.00

20 Chewing this gum in the normal manner is an effective remineralizing treatment for demineralized teeth.

EXAMPLE III

25 A mouthwash composition of the present invention is prepared according to the following formula:

	Ingredient	Parts by Weight
	Glycerine	30.00
	Flavour	0.1
30	Polyoxyethylene (20) sorbitan monoisostearate	0.5
	Na ₂ HPO ₄	0.37
	Sodium fluoride	0.04
	Calcium chloride	0.5
35	Indium (III) chloride	0.034
	Saccharin	0.05
	Citric acid	1.50
	Absolute alcohol	balance to 100

40 WHAT WE CLAIM IS:—

1. An anhydrous composition for the remineralizing of demineralized dental enamel comprising:

45 (A) a calcium salt having a solubility in water of at least 0.07% by weight at 100°C;

(B) a phosphate salt (as hereinbefore defined) having a solubility in water of at least 0.07% by weight at 100°C; and

50 (C) the balance, anhydrous ingredients suitable for use in the oral cavity; wherein the molar ratio of calcium to phosphate is from 0.01:1 to 100:1, and wherein said composition, when dispersed in water at a concentration of 1 part by weight of composition to 2 parts by weight of water, produces a pH of from 2 to 5.

2. A composition according to Claim 1, in

which the amount of the said water-soluble calcium salt is from 0.005% to 10% by weight and the amount of the said water-soluble phosphate salt is from 0.005% to 10% by weight.

3. A composition according to Claim 1 or 2, in which the molar ratio of calcium to phosphate is from 0.2:1 to 5:1.

4. A composition according to any of the preceding claims containing, as an additional ingredient, from 0.005% to 5% by weight of a salt of magnesium or a heavy metal (as hereinbefore defined), said salt having a solubility in water of at least 0.07% by weight at 100°C.

5. A composition according to Claim 4, in which the heavy metal is selected from manganese, tin, zinc, indium, aluminium, zirconium, iron, titanium, vanadium and the rare earth metals.

6. A composition according to Claim 5 containing, as an additional ingredient, from 0.005 to 5% of a salt (having a solubility in water of at least 0.07% by weight at 100°C) of an anion capable of forming a water-insoluble precipitate with the cations of calcium, magnesium or the heavy metals recited in Claim 5.

7. A composition according to Claim 6 where the said anion is fluoride.

8. A composition according to Claim 7 where the heavy metal is indium.

9. A composition according to Claim 2 or to any of Claims 3 to 8 as appendant to Claim 2, in the form of an anhydrous dentifrice which comprises from 0.5% to 50% by weight of a dentifrice abrasive, from 0.2 to 5% by weight of an organic surfactant and from 40% to 90% by weight of a humectant.

10. A composition according to Claim 2 or to any of Claims 3 to 8 as appendant to Claim 2, in the form of an anhydrous mouthwash which comprises from 5% to 90% by weight of an edible polyhydric alcohol and from 5% to 90% by weight of absolute alcohol.

11. A composition according to Claim 2 or to any of Claims 3 to 8 as appendant to Claim 2 in the form of an anhydrous chewing gum comprising a chewing-gum base.

12. An anhydrous composition for remineralizing demineralized dental enamel, substantially as herein described in Example I, II or III.

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